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REVIEW ARTICLE

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Autoimmune-associated hemophagocytic syndrome

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Abstract Hemophagocytic syndrome (HPS) is a clinicopathological condition characterized by the activation of histiocytes with prominent hemophagocytosis in bone marrow and other reticuloendothelial systems. The occurrence of HPS is usually associated with underlying disorders such as infection and lymphoma. Recently, we described patients with autoimmune disease who developed HPS. In these cases there was no evidence of underlying infection and malignancy, and the occurrences of HPS were associated with active autoimmune disease. Based on these observations, we described autoimmune-associated hemophagocytic syndrome (AAHS). This disease entity is becoming better known, and case reports presenting features compatible with clinical AAHS are increasing. Here, we review the clinical aspects, mechanisms, diagnosis, and treatment of AAHS according to our data and that in the literature.

Key words Autoimmune-associated hemophagocytic syndrome (AAHS) · Autoimmune disease · Hemophagocytic syndrome (HPS) · Hemophagocytosis

Introduction

Histiocytic phagocytosis is an important process in the elimination of effete and apoptotic blood cells from the circulation. However, dysregulated activation of histiocytes sometimes results in extensive hemophagocytosis, causing hemophagocytic syndrome (HPS). HPS is a clinicopathological condition characterized by the activation of histiocytes with prominent hemophagocytosis in bone marrow and other reticuloendothelial systems. The clinical characteristics of this syndrome include high fever, hepatosplenomegaly, pancytopenia, liver dysfunction, coagulopathy, and hyperferritinemia. HPS usually occurs in association with various underlying disorders such as infection, lymphoma, and autoimmune disease.

In this article, we review the clinical aspects, mechanisms, diagnosis, and treatment of HPS, focusing especially on autoimmune-associated hemophagocytic syndrome (AAHS) in relation to our own cases and those in the literature.

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History and classification of HPS

In 1939, Scott and Rob-Smith[1] reported a neoplastic disorder characterized by hemophagocytosing histiocytes and systemic proliferation of the precursors of histiocytes. This disorder was described as histiocytic medullary reticulosis (HMR), and was characterized by fever, lymphadenopathy, hepatosplenomegaly, and pancytopenia. HMR may be the first report of HPS, and it was succeeded by the disease entity known as malignant histiocytosis (MH), which was subsequently reported by Rappaport.[2]

In 1952, familial hemophagocytic reticulosis (familial hemophagocytic lymphohistiocytosis; FHL) was reported by Farquhar and Claireaux.[3] FHL occurs in infants, and is now regarded as primary HPS.

In 1979, Risdall et al.[4] reported the cases of 19 patients with active viral infection, whose bone marrow showed histiocytic hyperplasia with prominent hemophagocytosis. These cases showed high fever, constitutional symptoms, liver dysfunction, coagulation abnormalities, peripheral blood cytopenias, hepatosplenomegaly, and lymphadenopathy. They proposed that this condition should be called virus-associated hemophagocytic syndrome (VAHS), which is distinct from MH as a neoplastic disease. VAHS is

the first report of reactive or secondary HPS. Five years later, Risdall et al.[5] also reported some cases with reactive HPS which were associated with bacterial infections. This condition was called bacteria-associated hemophagocytic syndrome (BAHS). To date, reactive HPS has been reported to be associated not only with virus and bacteria infection, but also with various types of disseminated infections such as tuberculosis, fungi, and parasites.[6–13] Thus, HPS associated with underlying infection is collectively called infection-associated hemophagocytic syndrome (IAHS).

The origin of the proliferating cells in MH has been thought to be the precursors of histiocytes, but this remained largely unclear. Since 1981, cases with lymphoma resembling MH have been reported. Kadin et al.[14] have reported erythrophagocytic T gamma lymphoma resembling malignant histiocytosis. Jaffe et al.[15] have also described six patients with malignant lymphoma which mimicked MH, in which disseminated lymphoma cells were segregated from the phagocytic process, and the phagocytic cells had characteristics of histiocytes. Following these reports, many cases with lymphoma showing hemophagocytosis have been described. In most of these cases, it has been proved that the proliferating cells were not the precursors of histiocytes, but were lymphoma cells in themselves. Cases of "true MH," which is recognized as the neoplastic disease of immature histiocytes, is therefore now thought to be very rare, and reactive HPS associated with lymphoma, which resembles MH, is termed lymphoma-associated hemophagocytic syndrome (LAHS). Many T cell- or NK cell-type LAHS cases have been primarily reported,[16–20] and reports of B cell-type LAHS (B-LAHS) have been increasing. Recently, Takahashi et al.[21,22] reported that B-LAHS were found in 68 of 142 LAHS cases (48%) in Japan. In LAHS, nasal-type NK/T-cell lymphoma with angiocentric immunoproliferative lesions (AILs) and hepatosplenic T/NK-cell/B-cell lymphoma, with or without intravascular lymphomatosis (IVL), are important as underlying lymphoma.

The occurrence of reactive HPS has been reported to be associated with other malignancies such as myelodysplastic syndrome, multiple myeloma, acute leukemia, melanoma, and hepatocellular carcinoma,[23–31] and these conditions are called malignancy-associated hemophagocytic syndrome (MAHS). In addition, other underlying miscellaneous diseases have been described as the cause of reactive HPS.[32–35]

In 1991, Wong et al.[36] reported cases of patients with active SLE who demonstrated reactive hemophagocytosis in bone marrow. The occurrence of hemophagocytosis was associated with the activity of SLE itself, and they proposed a disease entity of acute lupus hemophagocytic syndrome (ALHS). In 1995 and 1997, we reported cases of reactive HPS which were associated with autoimmune diseases other than SLE, and proposed a new disease entity, autoimmune-associated hemophagocytic syndrome (AAHS).[37,38] Since then, the concept of AAHS has become more widely known, and case reports of AAHS are now accumulating.[39–54]

Table 1. Classification of HPS

1. Primary HPS
   Familial hemophagocytic lymphohistiocytosis (FHL)
2. Secondary (reactive) HPS
   1) Infection-associated hemophagocytic syndrome (IAHS)
      - Virus-associated hemophagocytic syndrome (VAHS)
      - Bacteria-associated hemophagocytic syndrome (BAHS)
      - Other: e.g., fungal, malaria, leishmaniasis, histoplasmosis, toxoplasmosis, tsutsugamushi diasease
   2) Malignancy-associated hemophagocytic syndrome (MAHS)
      - Lymphoma-associated hemophagocytic syndrome (LAHS)
      - Other: e.g., multiple myeloma, acute leukemia, mycosis fungoidosis, melanoma, hepatocellular carcinoma
   3) Autoimmune-associated hemophagocytic syndrome (AAHS)
   4) Other
      - Drug-associated
      - Miscellaneous underlying disease; e.g. Kawasaki disease, Kikuchi's disease, Chediak-Higashi disease

As a result of these historical and current findings, HPS is now classified as shown in Table 1. Primary HPS is known as FHL. Secondary (reactive) HPS occurs at all ages, and its occurrence is associated with various underlying disorders or clinical conditions.

Clinical features of HPS

In the cases with VAHS reported by Risdall et al.,[4] high fever, constitutional symptoms, liver dysfunction, coagulation abnormalities, and peripheral blood cytopenias were characteristic findings. In particular, fever was found in all patients and 79% showed pancytopenia (Table 2). Reiner and Spivak[55] described the clinical features of 23 cases with hemophagocytosis (hemophagic histiocytosis), and found there were underlying infections in most cases. In their report, fever was observed in all patients, and lymphadenopathy, hepatomegaly, splenomegaly, and skin rash were relatively common. Of the laboratory features, anemia, leukopenia, and thrombocytopenia were often present. All patients had suppression of at least two lineages of hematopoietic cells, and 74% of patients had pancytopenia. Coagulopathy was observed in 52% of patients, and abnormalities in liver function were found in 87%. In Table 2, the clinical features of the adult cases reported by Tsuda[56] are also listed.

Esumi et al.[57,58] reported that serum ferritin markedly increased in the majority of patients with VAHS, as well as those with MH, and thus hyperferritinemia was suggested to be a useful marker of HPS. On the other hand, monocytes accumulate ferritin intracellularly during differentiation toward the macrophages, and macrophages release ferritin rapidly during the process of hemophagocytosis,[59,60] suggesting that hyperferritinemia in HPS is reflected by the activation of reticuloendothelial systems.

Between 1993 and 2003, we found 17 patients with autoimmune disease or rheumatic disease who demonstrated histiocytic hemophagocytosis in bone marrow. In

Table 2. Clinical features of HPS

	Risdall et al.[4]	Reiner and Spivak[55]	Tsuda[56]
Number of patients	19	23	23
Age (years)	nb[a]-61	22–77	21–78
Physical signs			
Fever	100%	100%	100%
Lymphademopathy	21%	48%	70%
Hepatomegaly	53%	39%	
Splenomegaly		35%	
Hepatosplenomegaly			35%
Rash	21%	26%	26%
Laboratory findings			
Pancytopenia	79%	74%	
Leukopenia (WBC)	100%[b]	78%	3.63[d]
Anemia (Hb)	100%[c]	100%	9.3[e]
Thrombocytopenia (Plt)	79%	91%	79[f]
Coagulopathy	68%	52%	30%
Liver dysfunction	74%	87%	48%

[a] nb, newborn; WBC, white blood cell counts; Hb, hemoglobin; Plt, platelet counts
[b] Leukopenia is defined as WBC $<4.5 \times 10^9$/l
[c] Hemoglobin (Hb) levels ranged from 5.1 to 9.7 g/dl (median 8.0). All patients showed decreased levels of Hb below 10 g/dl (100%), and 17 patients showed Hb $\leqq$ 9 g/dl (89%)
[d] Mean WBC, range 0.5–14.5 $\times 10^9$/l
[e] Mean Hb (5.1–12.9 g/dl)
[f] Mean platelet count (5–24.8 $\times 10^9$/l)

these patients, a complication of infection or malignancy was excluded as the cause of hemophagocytosis, and hemophagocytosis occurred concomitantly during the active phase of disease, indicating that the occurrence of hemophagocytosis is associated with autoimmune disease or rheumatic disease itself. Their clinical features are summarized in Tables 3 and 4.

As summarized in Table 3, high fever and hyperferritinemia, which have been reported to be characteristic findings of IAHS or LAHS, were not always observed. Three (cases 1, 4, and 7) of 17 patients (18%) did not show fever, which was not developed after the presentation. In cases 2, 3, 5, 8, 9, and 14, who showed low fever, no further rise in body temperature was noted. Four patients (cases 1 and 4–6; 24%) demonstrated a normal range of serum ferritin. No remarkable changes in levels of ferritin were revealed during the courses of the cases that showed normal or mild elevation of ferritin levels. Cases 11–13 showed further increases in ferritin levels until the start of therapy, concomitantly with the rapid decrease of WBC and/or platelet count (Table 3).

Cytopenia affecting more than two lineages in the peripheral blood was observed in 12 of 17 patients (71%). In cases 1 and 8, WBC count and hemoglobin levels were further decreased after admission. Coagulopathy was not evident in any cases. The bone marrow cellularity of the patients was heterogeneous. Nine patients showed a hypocellular bone marrow. Among these, three cases (cases 1, 8, and 13) developed to severe marrow aplasia.

On the other hand, four patients had underlying SLE (cases 5, 6, 9, and 10). Cytopenia, including anemia, leukopenia or lymphopenia, and thrombocytopenia, are frequent manifestations of SLE, but pancytopenia occurs in fewer than 10% of patients.[61] If pancytopenia is present in SLE, it is often mild.[61] Larson[62] reported that 18% of 200 patients with SLE had leukocyte counts below 4.5×10^9/l, and that the usual range of leukopenia was between 2.5 and 3.5×10^9/l. Severe leukopenia, with counts of below 2×10^9/l, was uncommon. In a report by Wong et al.[36] about patients with ALHS, five of six patients had leukopenia, with leukocyte counts of below 2×10^9/l. Tsuboi et al.[50] have described three patients who developed HPS associated with SLE, and all had severe leukopenia (between 1.2 and 2.2×10^9/l). Similarly, Moriguchi et al.[52] reported a case with HPS associated with SLE who showed severe leukopenia (1.7×10^9/l). Therefore, the presentation of severe leukopenia or pancytopenia accompanying hemophagocytosis is not a recognized manifestation of SLE.[36] Therefore, if severe leukopenia or pancytopenia develop in a patient with SLE, the possibility of the complication of HPS should be considered.

Possible mechanisms of AAHS

The mechanism inducing reactive HPS is not fully understood. However, immunological dysregulation associated with underlying disease may be critically involved. Some possible mechanisms inducing AAHS are shown schematically in Fig. 1.

Considerable evidence suggests that cytokines play an important role in inducing reactive HPS.[63–70] In VAHS or LAHS, it has been suggested that cytokines secreted by virus-infected T lymphocytes or lymphoma cells activate histiocytes to induce hemophagocytosis.[68–70] In fact, TNF-α, IFN-γ, IL-1, IL-2, IL-6, IL-8, and M-CSF have been reported to be elevated by various degrees in the serum of

Table 3. Clinical features of patients with hemophagocytosis associated with autoimmune disease

Patient	Underlying disease	Age (years)	Sex	Fever (°C)	Lymph-adenopathy	Hepato-megaly	Spleno-megaly	WBC ($\times 10^9$/l)	Hb (g/dl)	Plt ($\times 10^9$/l)	DIC	Liver dysfunction	CRP (mg/dl)	Ferritin (μg/l)	Autoantibodies	Possible mechanism (main mechanism)
1	Evans	60	M	36	−	−	−	2.2	12.2	2	−	−	6.1	245	Anti-neutrophil Ab, cold hemagglutinin, PA/PB-IgG	Autoantibody
2	SSc	66	M	37	+	−	−	3.3	11.2	78	−	+	10	286	Cold hemagglutinin, PA-IgG, ANA	Autoantibody
3	MCTD	64	F	37	+	−	+	4.4	11.9	33	−	−	0.2	278	PA-IgG, ANA, RNP	Autoantibody
4	Felty	64	F	36	−	−	+	1.9	10.5	111	−	−	4	69	Anti-neutrophil Ab, PA-IgG, RF	Autoantibody
5	SLE	48	F	37	−	+	−	3.1	9.9	145	−	−	0.2	34	SS-A, RNP	Autoantibody
6	SLE	25	F	38	−	−	−	2.9	9.8	15.9	−	−	0.2	71	Anti-DNA Ab, ANA, RNP	Autoantibody
7	SS	70	F	36	−	−	−	2.9	10	149	−	−	0.2	496	PA-IgG, D-Coombs, SS-A	Autoantibody
8	RA	69	F	37	−	−	−	1.5	10.3	19	−	−	0.4	395	RF, PAIgG	Autoantibody (+cytokine)
9	SLE	29	M	37	−	+	+	2.1	9.3	72	−	−	1.3	1745	PA-IgG, D-Coombs, Anti-DNA Ab	Cytokine
10	SLE	29	F	40	+	+	+	2.2	10.9	142	−	+	0.2	2331	Anti-DNA Ab, ANA	Cytokine
11	PN	82	F	38	−	−	−	13.1 → 5.7	9.4	26.6	−	−	7	2155 → 14000	PAIgG, MPO-ANCA	Cytokine
12	AOSD	55	F	38	−	+	−	24.8 → 3.7	10.8	36.8 → 14.2	−	+	11.3	1635 → 6040	−	Cytokine
13	AOSD	46	F	38	−	+	+	14 → 3.7	7.6	82	−	+	1.1	31815	−	Cytokine
14	AOSD	50	F	37	−	+	+	2.1	9.8	12	−	+	0.8	8038	−	Cytokine
15	AOSD	38	M	38	−	+	−	23	14.1	31.2	−	+	11.7	2164	−	Cytokine
16	AOSD	20	M	38	+	+	+	24.7	13.3	16.9	−	+	7.3	13000	−	Cytokine
17	AOSD	66	F	39	+	−	−	2.8	10.6	76	−	+	11.6	39602	−	Cytokine

Evans, Evans' syndrome (resembling Evans' syndrome, patient had multiple autoantibodies against trilineage hematopoietic cells, but Coomb's test was negative); SSc, systemic sclerosis; MCTD, mixed connective tissue disease; Felty, Felty's syndrome; SLE, systemic lupus erythematosus; SS, Sojren's syndrome; RA, rheumatoid arthritis; PN, polyarteritis nodosa (myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA)-positive vasculitis); AOSD, adult-onset Still's disease; WBC, white blood cell counts; Hb, hemoglobin; Plt, platelet counts; DIC, disseminated intravascular coagulation; PA/PB-IgG, platelet-associated/-binding IgG; ANA, antinuclear antibodies; RNP, anti-RNP antibodies; D-Coomb, direct Coomb's test; RF, rheumatoid factor; SS-A, anti SS-A antibodies

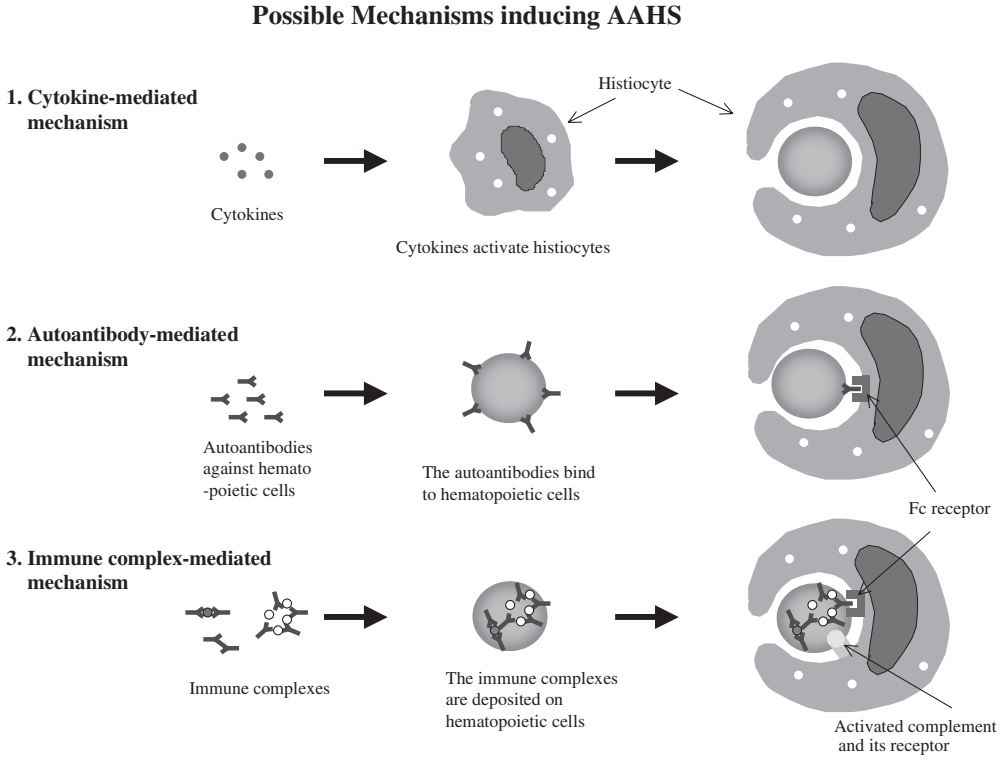

Fig. 1. Possible mechanisms inducing AAHS. 1. Cytokine-mediated mechanism. Inflammatory cytokines are produced in association with abnormal immune responses of underlying autoimmune disease. The cytokines stimulate histiocytes, resulting in hemophagocytosis. This mechanism is consistent with that of IAHS and LAHS. 2. Autoantibody-mediated mechanism. Autoantibodies directed against hematopoietic cells are produced and bind to the specific hematopoietic cells. These sensitized hematopoietic cells are recognized and phagocytosed by histiocytes via binding of the Fc portion of the antibodies and Fc receptor on histiocytes (ADCC). 3. Immune-complex-mediated mechanism. The deposition of circulating immune complexes on the marrow hematopoietic cells results in histiocytic hemophagocytosis through the binding of the antibody in the complexes, or activated complements to the receptors on histiocytes

Table 4. Clinical features of patients with hemophagocytosis associated with autoimmune disease

	Number (%)
Physical signs	
Fever	
≧ 37°C	6/17 (47%)
≧ 38°C	8/17 (44%)
Lymphadenopathy	5/17 (29%)
Hepatomegaly	8/17 (47%)
Splenomegaly	7/17 (41%)
Laboratory data	
WBC $< 4 \times 10^9$/1	10/17 (59%)
Hb < 10 g/dl	7/17 (41%)
Plt $< 100 \times 10^9$/1	8/17 (47%)
Cytopenia ≧ 2 lineages	12/17 (71%)
Coagulopathy (DIC)	0/17 (0%)
Elevation of AST/ALT	8/17 (47%)
Hyper CRP-nemia	13/17 (76%)
Hyperferritinemia	14/17 (82%)

patients with hemophagocytosis, but not all these cytokines are strongly elevated in each case. As for cases with VAHS or LAHS, a cytokine-mediated mechanism seems to be involved in cases of AAHS.

As shown in Table 3, cases 1, 2, and 3 had specific autoantibodies directed against hematopoietic cells. An autoantibody-mediated mechanism as the mechanism inducing histiocytic hemophagocytosis is suggested in these cases.[37,38] In this mechanism, hematopoietic cells are sensitized by autoantibodies and phagocytosed by histiocytes through the binding of the Fc portion of the antibodies to Fc receptors on histiocytes (antibody-dependent cellular cytotoxicity; ADCC). There is substantial evidence that the extrinsic administration of antineutrophil antibodies causes phagocytosis of neutrophils by macrophages in bone marrow and lymphoid organs in experimental models of autoimmune neutropenia.[71,72] Furthermore, it has been reported that IgG-coated hematopoietic cells are phagocytosed by macrophages and other cells through expressing Fcγ receptors.[73] Therefore, autoantibodies directed against hematopoietic cells might be responsible for the mechanisms causing histiocytic hemophagocytosis. In a case with Felty's syndrome, we observed phagocytosis of neutrophils by histiocytes in the bone marrow (case 4), in which neutrophil-phagocytosis may occur via an autoantibody (antigranulocyte antibody)-mediated mechanism.[51]

Wong et al.[36] favored an immune-complex-mediated mechanism as the pathogenesis of ALHS. They speculated that the deposition of circulating immune-complex on the marrow hematopoietic cells results in histiocytic hemophagocytosis through the binding of the antibody in the

complex or activated complements to the receptors on histiocytes. This mechanism seems to be involved in cases that show high titers of circulating immune-complex or low serum complement level.

There have been several reports suggesting cytokines as the pathogenesis of HPS that is associated with SLE. We found an elevation of serum levels of IL-1β without a low serum complement level in SLE-associated HPS, suggesting the possible involvement of IL-1β as the pathogenesis of HPS.[41] In other reports, cytokines such as IFN-γ, TNF-α, IL-1β, IL-6, sIL-2R, and M-CSF were suggested to be involved in the pathogenesis of SLE-associated HPS.[50,52] In these cases, the shifting of T helper 2 (Th2) to Th1 immune responses probably leads to the production of Th1 cytokines, inducing HPS. Therefore, not only autoantibodies or immune-complexes, but also cytokines, might contribute to the development of HPS associated with SLE.

It has been indicated that histiocytic/macrophagic phagocytosis is critically involved in the clearance of apoptotic cells to maintain tissue homeostasis.[74–78] Several molecules associated with phagocytosis of apoptotic cells have been identified, and these include phosphatidylserine, vitronectin, thrombospondin, CD36, CD14, β2 integrin, antiphospholipid antibodies, anti-β2-glycoprotein 1 (β2GP1) antibodies, lectin, macrophage scavenger receptors, and the newly found milk fat globule-EGF-factor 8.[74,79–91] These molecules were suggested to be associated with the clearance of apoptotic cells, and it would be interesting to investigate whether they are also involved in the pathogenesis of HPS. In fact, Sekigawa et al.[48] reported cases of hemophagocytosis who had high levels of anti-β2GP1 antibodies and anticardiolipin antibodies, and suggested a possible role of these antibodies in the pathogenesis.

In cases of HPS, marrow hypoplasia sometimes develops. Marrow hypoplasia may be mediated not only via hemophagocytosis by histiocytes, but also via the suppression of hematopoiesis by cytokines. TNF-α and IFN-γ, which are involved in the pathogenesis of HPS, are also known to inhibit hematopoietic colony formation in vitro.[92] These cytokines activate the expression of Fas receptor on $CD34^+$ hematopoietic stem cells in aplastic anemia.[93] The activation of Fas receptor by its ligand presenting on T cells might initiate apoptosis in the Fas receptor-expressing $CD34^+$ cells.[94] In addition, the elevation of soluble Fas ligand (sFasL) in the serum of patients with HPS has been reported.[95] Therefore, cytokines such as TNF-α and IFN-γ may be associated with the suppression of hematopoiesis via the Fas receptor/Fas ligand system, as indicated in aplastic anemia.[96]

Relationship between clinical features and mechanisms

As summarized in Tables 3 and 4, the clinical features of patients with autoimmune disease who showed concomitant hemophagocytosis are heterogeneous. High fever and hyperferritinemia were not always found. Patients who did not show high fever and hyperferritinemia had various autoantibodies against hematopoietic cells. While patients who did show high fever and hyperferritinemia also showed elevated levels of serum cytokines such as IL-1β, IL-6, and M-CSF, but not the presence of autoantibodies against hematopoietic cells. Therefore, we hypothesize that these differences in clinical features may depend on the mechanism underlying hemophagocytosis.[97] The cause of high fever and hyperferritinemia, as observed in cases with IAHS and LAHS, could be explained as the physiological activities of inflammatory cytokines, which are simultaneously causative for the activation of histiocytes. On the other hand, in autoantibody- or immune complex-mediated mechanisms, the activation of cytokines may not be primarily involved, resulting in the absence of systemic symptoms. This hypothesis should be studied further based on a larger series of patients.

Diagnosis of AAHS

Diagnostic criteria for HPS have already been proposed by Henter et al.,[98] Imashuku,[67] and Tsuda[56] (Table 5). These criteria do not seem to be suitable for the diagnosis of AAHS, since the clinical features of AAHS are not absolutely the same as those of other reactive HPS. Therefore, we show the important points for the diagnosis of AAHS in Table 5D. A diagnosis of AAHS requires the presence of cytopenia affecting at least two lineages in the peripheral blood, and the pathological finding of histiocytic hemophagocytosis in reticuloendothelial systems. In addition to these two points, a diagnosis of AAHS needs to ensure that HPS occurs in the active phase of the underlying autoimmune disease, since an occurrence of AAHS is usually dependent on the disease activity. If HPS develops in the inactive phase of disease, the possibility of other reactive HPS, such as IAHS, should be extensively investigated. It is also necessary to exclude other reactive HPS, such as LAHS. All these four points must be fulfilled before a diagnosis of AAHS is made. In addition, autoantibodies against hematopoietic cells, including antineutrophil antibody or platelet-associated IgG, sometimes develop in cases of autoantibody- or immune complex-mediated AAHS. In these cases, high fever and hyperferritinemia are usually absent.

Hemophagocytosis can often be found in bone marrow of disorders other than HPS. In individuals showing no evidence of bone marrow disease or abnormalities, or severe and generalized disease (e.g., rheumatoid arthritis, disseminated carcinoma, or fever), erythrophagocytosis in bone marrow has been reported to a low or modest degree.[99] In cases with myelodysplastic disorder or myeloproliferative disorders, hemophagocytosis by marrow histiocytes can be observed to some extent (personal observation). Furthermore, it has been observed that terminally differentiated leukemia cells are phagocytosed by histiocytes in bone marrow.[100] In these cases, hemo-

Table 5. Diagnostic criteria for HPS

A. Diagnostic criteria for HLH proposed by Henter et al.[98]
   1. Clinical and laboratory criteria
      Fever (duration ≧ 7 days, with peaks ≧ 38.5°C)
      Splenomegaly (≧ 3 cm below the costal arch)
      Cytopenia (affecting ≧ 2 of 3 lineages in the peripheral blood and not caused by a hypocellular or dysplastic bone marrow):
        ANC ≦ 1.0×10^9/l, Hb ≦ 9 g/dl, PLT ≦ 100×10^9/l.
      Hypertriglyceridemia and/or hypofibrinogenemia
        Fasting TG ≧ 2.0 mmol/l or ≧ 3 SD of the normal value for age
        Fibrinogen ≦1.5 g/l or ≦ 3 SD
   2. Histopathological criteria
      Hemophagocytosis in bone marrow or spleen or lymph nodes
      No evidence of malignancy

B. Diagnostic criteria for HPS including secondary HPS proposed by Imashuku[67]
   1. Clinical and laboratory criteria
      Fever (duration ≧ 7 days, with peaks ≧ 38.5°C)
      Cytopenia (affecting ≧ 2 of 3 lineages in the peripheral blood and not caused by a hypocellular or dysplastic bone marrow):
        ANC ≦ 1.0×10^9/l, Hb ≦ 9 g/dl, PLT ≦ 100×10^9/l.
      Hyperferritinemia and/or hyper-LDH-nemia
        Ferritin ≧ 3 SD of the normal value for age, generally ≧ 1000 ng/ml
        LDH ≧ 3 SD of the normal value for age, generally ≧ 1000 IU/l
   2. Histopathological criteria
      Hemophagocytosis in bone marrow or spleen or lymph nodes
      Large granular lymphocytes, mature and immature, are often increased in number

C. Diagnostic criteria for HPS proposed by Tsuda[56]
   1. High fever for more than a week
   2. Unexplained progressive cytopenia affecting at least two cell lineages
   3. Bone marrow showing mature histiocyte ≧ 3% or 2500 cells/μl with prominent hemophagocytosis and/or hemophagocytosis in liver, spleen or lymph nodes
      # A diagnosis of HPS requires that all of the above criteria be fulfilled
      # A thorough search for familial history, initiating infections, malignancies and immunosuppressive states should be performed

D. Diagnostic criteria for AAHS proposed by Kumakura
   1. Cytopenia (affecting ≥ 2 of 3 lineages in the peripheral blood and not caused by an aplastic or dysplastic bone marrow)
   2. Histiocytic hemophagocytosis in bone marrow or other reticuloendothelial systems including spleen, liver or lymph nodes
   3. Active phase of underlying autoimmune disease at the occurrence of hemophagocytosis
   4. Other reactive hemophagocytic syndrome such as virus- or malignancy-associated hemophagocytic syndrome is excludable

Note:
Autoantibodies against hematopoietic cells sometimes develop
High fever, hyperferritinemia, and hyper-LDH-nemia are not always complicated

phagocytosis may be physiologically implicated in the clearance of aged or apoptotic cells from the circulation, and thus it is important to clarify what is distinctive, or what are sufficient numbers of hemophagocytic histiocytes in bone marrow, to diagnose HPS. Favara[101] stated that, "No quantitative data are available, but if careful study of three or more smears fails to demonstrate an average of at least two hemophagocytic cells per slide, one cannot be confident of the significance of finding that rare cell." On the other hand, Tsuda[56] defined the quantitative numbers of hemophagocytic histiocytes in marrow to diagnose HPS as ≧ 3%, or 2500 cells/μl, of mature histiocytes with prominent hemophagocytosis (Table 5C). However, it is not clear what are the distinctive or sufficient numbers of hemophagocytic histiocytes in bone marrow to diagnose AAHS. Therefore, the quantitative criteria need to be defined. Moreover, although in many cases with HPS the bone marrow initially shows hemophagocytosis, it is sometimes not shown and develops later in the course of the disease. Under circumstances in which the diagnosis of HPS is suspected but initial examinations have not shown hemophagocytosis, additional bone marrow examinations might be justified before a diagnosis of HPS.[101]

Treatment of AAHS

The treatment strategies for AAHS are not well established, but most cases are treated with immunosuppressive agents with a relatively good response. In our cases, all patients were receiving immunosuppressive agents, as shown in Table 6. The initial therapies included high-dose corticosteroid therapy (prednisolone 1 mg/kg/day), methylprednisolone (mPSL) pulse therapy (mPSL 1 g/day for 3 days), and a half-dose of mPSL pulse therapy (mPSL 0.5 g/day for 3 days). Case 1 was refractory to various treatments, including steroid therapy and splenectomy, but the administration of vincristine (VCR) achieved good results.[37] In case 2, steroid therapy and cyclophosphamide (CPA) pulse therapy (CPA 500–700 mg/day for 1 day) showed a relatively good response, but the patient died of respiratory

Table 6. Therapies and outcomes of patients with hemophagocytosis associated with autoimmune disease

Patient	Underlying disease	Medication at onset of HPS	Therapy performed	Outcome
1	Evans	–	High dose PSL, mPSL pulse, CyA, splenectomy, plasma exchange, etoposide, ineffective; IVIg, G-CSF, transiently effective; eradication of H. pylori, transiently effective for thrombocytopenia; VCR, effective	Improved
2	SSc	Intermediate dose PSL	High-dose PSL, ineffective; CPA pulse, effective	Died*
3	MCTD	Low dose PSL	High-dose PSL, effective	Improved
4	Felty	NSAID	Half-dose of mPSL pulse, effective	Improved
5	SLE	Low dose PSL	High-dose PSL, effective	Improved
6	SLE	Low dose PSL	High-dose PSL, effective	Improved
7	SS	Low dose PSL	mPSL pulse, effective	Improved
8	RA	NSAID	mPSL pulse, G-CSF, cyclosporine A, transiently effective	Partially improved
9	SLE	Low dose PSL	mPSL pulse + G-CSF, effective	Improved
10	SLE	–	High-dose PSL, effective	Improved
11	PN	–		Improved
12	AOSD	Low dose PSL	High-dose PSL, ineffective; PSL + CPA, effective	Improved
13	AOSD	–	High-dose PSL, transiently effective; VCR + CPA, effective	Improved
14	AOSD	Low dose PSL	High-dose PSL, transiently effective; CPA pulse, effective	Improved
15	AOSD	–	High-dose PSL, ineffective; CPA pulse, effective	Improved
16	AOSD	–	mPSL pulse, effective	Improved
17	AOSD	–	mPSL pulse, transiently effective; PSL + MTX, effective	Improved

PSL, prednosolone; NSAID, nonsteroidal anti-inflammatory drug; mPSL, methylprednisolone; IVIg, intravenous immunoglobulin; G-CSF, granulocyte-colony stimulating factor; VCR, vincristine; CPA, cyclophosphamide; MTX, methotrexate
* Died of respiratory failure

failure due to pulmonary fibrosis.[38] Case 9, who showed severe neutropenia, was successfully treated with mPSL pulse therapy in addition to recombinant human granulocyte-colony stimulating factor (G-CSF) (5μg/kg/day) for 3 days.[41] Cases 12, 13, 14, and 15, which were refractory to steroid therapy, responded to CPA and/or VCR.[39] Case 17 partially responded to mPSL pulse therapy, but the patient improved by the additional treatment of methotrexate in combination with steroid therapy.

Treatment of AAHS is indicated for patients who have the active phase of the disease and show severe cytopenia or progression of cytopenia. The treatment consists of therapies for the underlying disease, as well as cytokine storm or autoantibody production. A standard treatment for AAHS has not yet been established, but most AAHS patients responded to immunosuppressive agents such as corticosteroids. In severe cases or cases that are refractory to high-dose corticosteroid therapy, a mPSL or CPA pulse is sometimes needed. Treatment with G-CSF is a reliable alternative, which will increase the neutrophil count in the majority of patients with neutropenia. G-CSF seems to be beneficial in some AAHS cases with severe or life-threatening neutropenia. Other therapies include cyclosporine A, high-dose intravenous immunoglobulin G (IVIg), plasma exchange, and cytotoxic agents.[43,50] In one of our patients with AAHS who had life-threatening severe cytopenia and was refractory to various therapies, a successful response was obtained by the use of VCR.[37] In this case, autoantibodies against trilineage hematopoietic cells were found, and therefore VCR could suppress the histiocytic hemophagocytosis, as is the case with idiopathic thrombocytopenic purpura. This therapy, as well as IVIg, seems to be effective in cases whose hemophagocytosis is via an autoantibody-mediated mechanism (ADCC). More recently, a favorable effect from etoposide (VP16) was reported in the treatment of a severe and refractory AAHS case.[53]

Summary

We have described the clinical features, mechanisms, diagnosis, and treatment of AAHS. At the occurrence of reactive HPS, the possibility of autoimmune disease must be considered as one of the underlying diseases. In particular, when unexplained cytopenia progresses during the course of autoimmune disease, the physician should be aware of the possibility of HPS. In order to diagnose AAHS, it is necessary to rule out other reactive HPS such as IAHS. It has been shown that IAHS sometimes develops under the immunocompromized host, so it is essential to investigate whether or not there is an underlying infection in such a case.

Many unsolved problems remain, e.g., elucidation of the pathogenesis, and the establishment of exact diagnostic criteria and a specific therapy based on the pathogenesis. A full understanding of AAHS will require further studies.

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